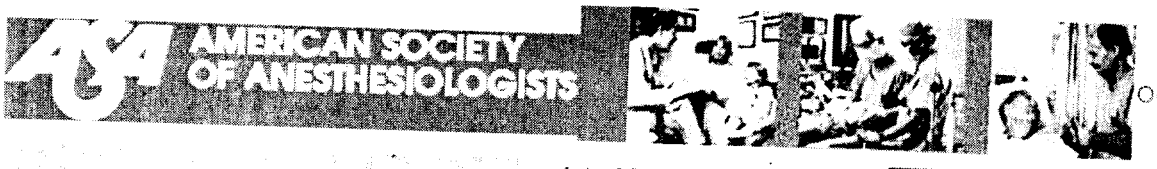




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# FDA Alert:

## Update on Droperidol and the FDA

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In December 2001, the Food and Drug Administration (FDA) placed a "black box" warning on droperidol labels because of serious concerns about its potential to cause life-threatening ventricular dysrhythmias. Droperidol has been shown to cause QTc prolongation, and in March 2001, worldwide marketing of droperidol outside the United States was discontinued following a risk-benefit analysis and examination of reported cases of QTc prolongation.

These events led the FDA to review its own postmarketing safety database, Janssen's analysis and the available literature on droperidol and QTc prolongation. Dose-dependent QTc prolongation and association with torsades de pointes (TdP) upon challenge and rechallenge with droperidol was well documented in the literature. In addition, the postmarketing safety database was found to contain cases of QTc prolongation, TdP, cardiac arrest and death associated with doses of droperidol at and below the lowest labeled dose of 2.5 mg.

Anesthesiologists typically use very low doses of droperidol for the treatment and prevention of nausea and vomiting — well below the lowest labeled dose of 2.5 mg. — and the potential for QTc prolongation at these low doses has not been well characterized. In order for the FDA to approve droperidol at doses below 2.5 mg, the Administration must be provided with data that satisfy regulatory requirements for the demonstration of efficacy and safety at these doses.

Droperidol has been a priority within the FDA as evidenced by its willingness to devote significant human and financial resources to continue the evaluation of the pharmacology and safety profile of this drug. A comprehensive evaluation of the postmarketing safety databases of droperidol and its alternatives has been undertaken, and the FDA sponsored a study recently that measured QTc prolongation after administration of droperidol to healthy volunteers.

The study utilized a crossover design with droperidol doses of 0 mg, 0.625 mg, 2.5 mg and 5 mg. Although the study was prematurely terminated because of significant neuropsychiatric

adverse effects, including dysphoria and anxiety, there were several findings of note. Impressive QTc prolongations (approximately 80 ms from baseline) were found in individuals following the 2.5 mg and the 5 mg doses, even though only seven and three subjects, respectively, received these doses. Compared to placebo, the 0.625 mg dose did not appear to have a significant effect on QTc; however, this cannot be considered a definitive finding as only five individuals were studied at this dose. Additional investigation will be required to further define the relationship between QTc prolongation, potential for dysrhythmia and various doses of droperidol.

The FDA is now exploring options to obtain data that satisfy regulatory standards for the demonstration of safety and efficacy at doses lower than 2.5 mg. An advisory committee meeting to discuss droperidol also is planned. We continue to closely follow the adverse events database for droperidol, and we urge practitioners to participate in the postmarketing safety assessment process by reporting all potential drug-related adverse events. For more information on reporting adverse events, visit **<www.fda.gov/medwatch>**.

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